at least moderate, and optionally, under high stringency conditions.

In a further embodiment, the isolated nucleic acid molecule comprises a polynucleotide that has at least about 90%, preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 1 to 839 of Figure 209 (SEQ ID NO:496); or at least about 90%, preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 1 to 1041 of Figure 211 (SEQ ID NO:498).

In a specific embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding native or variant PRO285 and PRO286 polypeptides, with or without the N-terminal signal sequence, and with or without the transmembrane regions of the respective full-length sequences. In one aspect, the isolated nucleic acid comprises DNA encoding a mature, full-length native PRO285 or PRO286 polypeptide having amino acid residues 1 to 1049 of Figure 209 (SEQ ID NO:496) and 1 to 1041 of Figure 211 (SEQ ID NO: 498), or is complementary to such encoding nucleic acid sequence. In another aspect, the invention concerns an isolated nucleic acid molecule that comprises DNA encoding a native PRO285 or PRO286 polypeptide without an N-terminal signal sequence, or is complementary to such encoding nucleic acid sequence. In yet another embodiment, the invention concerns nucleic acid encoding transmembrane-domain deleted or inactivated forms of the full-length native PRO285 or PRO286 proteins.

In another embodiment, the invention the isolated nucleic acid molecule comprises the clone (DNA40021-1154) deposited on October 17, 1997, under ATCC number 209389; or the clone (DNA42663-1154) deposited on October 17, 1997, under ATCC number 209386.

In yet another embodiment, the invention provides a vector comprising DNA encoding PRO285 and PRO286 polypeptides, or their variants. Thus, the vector may comprise any of the isolated nucleic acid molecules hereinabove defined.

In another embodiment, the invention provides isolated PRO285 and PRO286 polypeptides. In particular, the invention provides isolated native sequence PRO285 and PRO286 polypeptides, which in one embodiment, include the amino acid sequences comprising residues 1 to 1049 and 1 to 1041 of Figures 209 and 211 (SEQ ID NOS:496 and 498), respectively. The invention also provides for variants of the PRO285 and PRO286 polypeptides which are encoded by any of the isolated nucleic acid molecules hereinabove defined. Specific variants include, but are not limited to, deletion (truncated) variants of the full-length native sequence PRO285 and PRO286 polypeptides which lack the respective N-terminal signal sequences and/or have their respective transmembrane and/or cytoplasmic domains deleted or inactivated.

The invention also specifically includes antibodies with dual specificities, e.g., bispecific antibodies binding more than one Toll polypeptide.

In yet another embodiment, the invention concerns agonists and antagonists of the native PRO285 and PRO286 polypeptides. In a particular embodiment, the agonist or antagonist is an anti-PRO285 or anti-PRO286 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of the native PRO285 and PRO286 polypeptides.

In a still further embodiment, the invention concerns a composition comprising a PRO285 or PRO286 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically

acceptable carrier.

The invention further concerns a composition comprising an antibody specifically binding a PRO285 or PRO286 polypeptide, in combination with a pharmaceutically acceptable carrier.

The invention also concerns a method of treating septic shock comprising administering to a patient an effective amount of an antagonist of a PRO285 or PRO286 polypeptide. In a specific embodiment, the antagonist is a blocking antibody specifically binding a native PRO285 or PRO286 polypeptide.

84. PRO213-1, PRO1330 and PRO1449

The present invention concerns compositions and methods for the diagnosis and treatment of neoplastic cell growth and proliferation in mammals, including humans. The present invention is based on the identification of genes that are amplified in the genome of tumor cells. Such gene amplification is expected to be associated with the overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to be useful targets for the diagnosis and/or treatment (including prevention) of certain cancers, and may act as predictors of the prognosis of tumor treatment.

In one embodiment, the present invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO213-1, PRO1330 and/or PRO1449 polypeptide having amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector designated as DNA30943-1163 (ATCC 209791) deposited on April 21, 1998; DNA64907-1163-1 (ATCC 203242) deposited on September 9, 1998 and/or DNA64908-1163-1 (ATCC 203243) deposited on September 9, 1998.

In another embodiment, the present invention comprises an isolated nucleic acid molecule having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO213-1, PRO1330 and/or PRO1449 polypeptide having amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively; or (b) the complement of the DNA molecule of (a).

In another embodiment, the invention provides an isolated PRO213-1, PRO1330 and/or PRO1449 polypeptide. In particular, the invention provides isolated native sequence PRO213-1, PRO1330 and/or PRO1449 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), respectively. Optionally, the PRO213-1, PRO1330 and/or PRO1449 polypeptide is obtained or obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA30943-1163 (ATCC 209791), DNA64907-1163-1 (ATCC 203242) or DNA64908-1163-1 (ATCC 203243).

In another aspect, the invention provides an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 95% sequence identity to amino acid residues 1 to

295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), inclusive.

In yet another embodiment, the invention provides an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising the amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), or a fragment thereof sufficient to provide a binding site for an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody. Preferably, the PRO213-1, PRO1330, and/or PRO1449 fragment retains a qualitative biological activity of a native PRO213-1, PRO1330, and/or PRO1449 polypeptide.

In a further aspect, the invention concerns an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively.

In still a further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with: (a) a DNA molecule encoding a PRO213-1, PRO1330, and/or PRO1449 polypeptide having the amino acid residues from 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively; or the complement of the DNA molecule of (a), and if said test DNA molecule has at least about an 80% sequence identity to (a) or (b), (ii) culturing a host cell comprising said test DNA molecule under conditions suitable for the expression of said polypeptide, and (iii) recovering said polypeptide from the cell culture.

In one embodiment, the present invention concerns an isolated antibody which binds a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In one aspect, the antibody induces death of a cell overexpressing a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or an anti-idiotypic antibody.

In another embodiment, the invention concerns a composition comprising an antibody which binds a PRO213-1, PRO1330 and/or PRO1449 polypeptide in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In a further embodiment, the invention concerns nucleic acid encoding an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody, and vectors and recombinant host cells comprising such nucleic acid.

The invention further concerns antagonists and agonists of a PRO213-1, PRO1330 and/or PRO1449 polypeptide that inhibit one or more of the functions or activities of the PRO213-1, PRO1330 and/or PRO1449 polypeptide.

In a further embodiment, the invention concerns isolated nucleic acid molecules that hybridize to the complement of the nucleic acid molecules encoding the PRO213-1, PRO1330 and/or PRO1449 polypeptides. The nucleic acid preferably is DNA, and hybridization preferably occurs under stringent conditions. Such